A 6-Year Follow-up Study of Vagus Nerve Stimulation Effect on Quality of Life in Treatment-Resistant Depression
A Pilot Study

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Objectives: Treatment-resistant depression (TRD) carries a major burden on those affected by this disease and significantly impacts their quality of life (QOL). Vagus nerve stimulation (VNS) has showed promising results on symptoms, but its impact on QOL remains underresearched. This study aims to evaluate the long-term effects of VNS on both QOL and clinical symptoms for TRD patients, through a naturalistic 6-year follow-up.

Method: Outpatients with confirmed TRD were enrolled to receive VNS. None of the patients enrolled left the study or was lost at follow-up. Patients were evaluated at 1, 3, 6, 12, 24, 36, 48, 60, and 72 months for a total of 10 assessments using the 36 item Short Form questionnaire, Hamilton Rating Scale for Depression and Hamilton Anxiety Rating Scale.

Results: Ten patients were enrolled with a mean age of 50 years. This study shows a clinically and statistically significant improvement of the mental QOL ($P = 0.012$), physical QOL ($P < 0.002$), depressive symptoms ($P < 0.001$), and anxiety symptoms ($P < 0.001$).

Conclusions: This long-term naturalistic study is the first to demonstrate that the therapeutic effect of VNS on TRD goes beyond clinical symptoms to improve the daily QOL of those affected.

Key Words: treatment-resistant depression, vagal nerve stimulation, quality of life

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Affecting more than 300 million people, depressive disorders are the leading cause of years lived with disability according to the World Health Organization.[1] Major depressive disorder evolves in a chronic and/or recurrent pattern in 50% of the cases and shows no response to usual treatment in 15% to 30%, which is defined as treatment-resistant depression (TRD).[2] Vagus nerve stimulation (VNS) was shown to be efficacious for treatment of TRD and was Food and Drug Administration–approved in 2005.[3,4] A recent large 5-year observational study demonstrated VNS long-term effectiveness on clinical symptoms of TRD and even mortality.[5] However, TRD also impacts severely on the quality of life (QOL) of those affected by this disease, which is underresearched. Authors and guidelines now suggest focusing on treatment objectives beyond clinical symptoms to specifically address QOL.[6,7] A positive effect of VNS on the QOL of TRD patients has previously been reported for up to 2 years.[8–10] However, only few studies reported longer-term follow-up, even though it was showed that cumulative relapse rate is still significant after 2 years.[11,12] Longer-term effect of VNS on the QOL of TRD patients remains underresearched, or limited, and it is deemed important to address that specific issue.[13]

The purpose of this preliminary study is to evaluate the long-term effects of VNS on both clinical symptoms and QOL for TRD, through a 6-year naturalistic follow-up.

MATERIALS AND METHODS

This study reports data collected from the prospective naturalistic research project UMBRELLA: medical and technological database of the psychiatric Neuromodulation Unit of the Centre Hospitalier Universitaire de Montréal. Patients who began VNS treatment for TRD between November 2007 and April 2010 were included, after giving written formal consent, according to approved institutional Research Ethics Committee procedures. Treatment-resistant depression was defined as a major depressive episode, confirmed with Mini-International Neuropsychiatric Interview,[14] including bipolar depression, meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* Text Revision[15] criteria despite 3 antidepressant trials and at least 1 pharmacological potentiation.[16] The exclusion criteria were active neurological disorder, acute medical disorder, severe Axis II disorder, or another major Axis I disorder.

A baseline assessment was performed, and follow-up assessments were done at 1, 3, 6, 12, 24, 36, 48, 60, and 72 months for a total of 10 assessments. Quality of life was assessed with the 36 item Short Form questionnaire (SF-36), compiled using the standard method and Canadian normative data, which gives a mental health summary score (the mental component score [MCS]) and a physical health summary score (the physical component score [PCS]).[17,18] SF-36 has been psychometrically validated, with an internal consistency reliability estimated using Cronbach coefficient α of 0.89 for MCS and 0.94 for PCS.[19] Depression symptoms were evaluated with the Hamilton Depression Rating Scale (HDRS), 28 items.[20] Response is defined as a reduction of the HDRS total score greater than or equal to 50% of baseline score, and remission is defined as a score of less than or equal to 7. Anxiety symptoms were evaluated using the Hamilton Anxiety Rating Scale (HAM-A).[21]

Vagus nerve stimulation was administered through a Cyberonics model 102 pulse generator (Cyberonics Inc, Houston, Tex) consisting of a subcutaneous generator delivering automatic chronic intermittent stimulation through helicoidal electrodes around the left vagus nerve at the level of the neck. It was activated 10 days after implantation. Initial parameters were initiated

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at 0.25 mA output current and 30 Hz with 250 μs impulse duration. The stimulation duration was 30 seconds (*on*) with 5 minutes between stimulations (*off*). These parameters were modified during follow-up based on clinical response and tolerability to adverse effects. The treatment as usual (TAU) was continued, yet no change was permitted for the first year of VNS.

All analyses were conducted with IBM Corps SPSS version 21. Data are summarized as mean with 95% interval confidence for continuous variables and frequency for categorical variables. Repeated measures multivariate analysis of variance was performed on HDRS, HAM-A, MCS, and PCS, to account for dependent variables correlations. Repeated contrasts were used to make comparisons between different testing times.

RESULTS

Ten patients (6 women and 4 men) were recruited and followed for 72 months in this study, with a total of 400 data points. The mean age at the time of implantation was 50 years (SD, 4.7). Seven had a diagnosis of unipolar depression, and 3 had a diagnosis of bipolar depression. The mean number of depressive episode was 4 (SD, 1.3). None of the patients enrolled left the study or was lost at follow-up. The VNS treatment was globally well tolerated by patients.

Table 1 presents detailed results on symptoms scales and on QOL scores. Through the follow-up, we see a clinically and statistically significant improvement of HDRS score ($F_{9,81}$ = 14.745, P < 0.001) and HAM-A score ($F_{9,81}$ = 7.211, P < 0.001). For HDRS scores, a significant negative linear trend ($F_{1,9}$ = 60.593, P < 0.001) with a significant difference between baseline and first month evaluation ($F_{1,9}$ = 26.352, P = 0.001) were found. For HAM-A scores, a significant negative linear trend ($F_{1,9}$ = 36.761, P < 0.001) was found.

TABLE 1. Mean (95% Confidence Interval) of Rating Scales Through Follow-Up

		QOL (SF-36)		Symptom Rating Scales	
		MCS	PCS	HDRS	HAM-A
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Baseline		19.4 (11.7–27.0)	43.5 (35.8–51.2)	27.3 (23.2–31.4)	16.2 (11.0–21.4)
1 mo		28.0 (17.3–38.7)	42.35 (36.3–48.42)	16.0 (9.8–22.2)	9.7 (5.9–13.5)
3 mo		36.0 (24.7–47.4)	40.5 (30.0–51.1)	12.4 (6.4–18.4)	7.7 (5.2–10.2)
6 mo		33.5 (25.1–41.9)	45.3 (34.5–56.1)	10.1 (7.5–12.7)	7.5 (5.2–9.8)
12 mo		31.6 (20.5–42.7)	47.4 (39.4–54.2)	11.6 (4.3–18.9)	7.0 (3.6–10.4))
24 mo		36.0 (25.2–46.7)	47.4 (37.4–57.4)	10.1 (4.7–15.5)	7.0 (3.2–10.8)
36 mo		34.2 (23.6–44.8)	52.1 (45.3–58.8)	9.5 (5.0–14.0)	5.2 (2.8–7.6)
48 mo		36.0 (24.8–47.3)	49.9 (42.9–57.0)	9.1 (4.8–13.4)	6.3 (2.5–10.0)
60 mo		35.8 (25.0–46.5)	52.1 (47.3–56.9)	7.2 (3.7–10.7)	4.7 (2.4–7.0)
72 mo		38.7 (28.1–49.3)	50.9 (45.2–56.5)	7.9 (3.7–12.1)	6.2 (2.7–9.7)
Repeated measure MANOVA	*F*	3.479	14.745	7.211	3.479
	P	0.012	<0.002	<0.001	<0.001

MANOVA indicates multivariate analysis of variance.

We also report clinically and statistically significant improvement of MCS score ($F_{9,81}$ = 2.566, P = 0.012) and PCS score ($F_{9,81}$ = 3.479, P < 0.002). For MCS, a significant positive linear trend ($F_{1,9}$ = 5.973, P = 0.037) with a significant difference between the first month and the third month ($F_{1,9}$ = 5.839, P = 0.039) was found. For PCS, a significant positive linear trend ($F_{1,9}$ = 15.410, P = 0.003) was found.

Response was achieved by 30% of patients at 1 month, 70% at 12 months at 80% at 72 months, whereas remission was achieved by 30% of patients at 1 month, 50% at 12 months, and 50% at 72 months. Furthermore, 80% of patients are currently working, seeking employment, or volunteering.

DISCUSSION

Through the 6-year follow-up, we see a clinically and statistically significant improvement of both TRD depressive and anxiety symptoms. The significant difference between baseline and first month depressive scores suggests that improvement occurred earlier than previous VNS studies.[22] These preliminary results also suggest that VNS provides a higher remission rate than the 15% to 30% reported for repetitive transcranial magnetic stimulation (rTMS) and slightly lower the 50% to 60% remission rate reported for electroconvulsivotherapy (ECT).[23,24] The stability of the effect on both depressive and anxiety symptoms of TRD patients substantiates previous reports on the efficacious long-term management of TRD from VNS therapy.[4,25,26] Furthermore, 80% of patients achieved response and 50% remission, which is similar to the 60% to 80% response rate and 40% to 60% remission rate of previous VNS longer-term studies.[4,25,26]

Our study is the first one to report preliminary findings on the long-term VNS effect on the mental health QOL of depressed patients beyond 2 years. Previous studies provided a positive trend at 3, 12, and 24 months.[8–10,25] Our results suggest a clinically and statistically significant 6 years sustained improvement of the MCS with a significant positive linear trend and a significant difference between the first month and the third month. Vagus nerve stimulation effect on QOL seems to occur after the first month, whereas previous rTMS and ECT studies showed a faster improvement during this first month.[27–30] In this preliminary study, MCS improved of 100%, with 20% to 90% improvement reported in rTMS and ECT studies.[27–30] We report a sustained longer-term effect through the 6-year follow-up, which is not replicated in rTMS and ECT studies. Hence, VNS effect seems to help beyond depressive symptoms and has a long-term positive effect on the daily lives of affected patients. It is also of interest to note that 80% of the patients are currently working, seeking employment, or volunteering. As could be expected, PCS showed an improvement of less amplitude than its mental health counterpart. This was also shown in previous VNS, rTMS, and ECT studies.[9,27,30]

The small cohort size of 10 patients poses limitation to the precisions of our results, but it also reflects the difficulty to conduct long-term follow-up for the relatively few patients receiving VNS therapy. We can still present significant positive preliminary findings on QOL that substantiates previous studies of similar size.[25,31,32] The natural prospective design of the study also poses a limitation to the validity of the results because there was no sham control method, and without a control group, our findings are not definitive. Further comparison of our results to other studies is

limited because only few trials reported on the long-term effect of different treatments on QOL of TRD patients. One previous recent study comparing long-term psychoanalytic psychotherapy to TAU for TRD followed patients for 42 months.[33] They showed that QOL of the TAU group did not improve, and studies on the evolution of TRD with usual treatment show that only 20% of TRD will reach remission through long-term follow-up.[4,34] Furthermore, Aaronson's study showed that in the TAU group only 30% reach remission and 40% have response during the 5 years of follow-up.[5] Hence, we are inclined to think the improvement we report on both QOL and clinical symptoms reflects an effect of VNS treatment and not only the effect of time. Another limit comes from the concurrent usual pharmacological and psychological treatments. However, changes were only permitted after 1 year of VNS treatment and most improvement in our study occurred during the first year.

As such, we report positive preliminary findings suggesting a sustained long-term positive effect of VNS that goes beyond depressive symptoms to improve the QOL of TRD patients through a 6 year follow-up.

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